REMARKS

Applicants have canceled, without prejudice, claims 2-4. Applicants reserve the right to present the subject matter of those claims in applications claiming the benefit hereof. Applicants have also amended claims 1, 7, 15 and 48 to recite the preferred anticholinergic compounds of the invention: ipratropium and tiotropium and their salts (claims 1, 7 and 48) and a combination formulation (claim 15). Applicants have also added new claims 49-50. Support for the new claims may be found throughout the specification as filed, for example, on page 2, lines 9-13. No new matter has been added by any of the amendments.

In the Office Action in the parent case, claims 1, 5-9, 12-18, 21-22, 45 and 48-50 were "rejected under 35 U.S.C. §103(a) as being unpatentable over Reiss et al. (2002/0052312 A1) in view of Meissner et al. (2002/0115680 A1)". In particular, it was alleged to

> "have been obvious to a person of ordinary skill in the art at the time the invention was made, given the general teachings of Reiss on method of treating COPD by administering a combined therapy of anticholinergics such as tiotropium bromide and a dopamine agonist to have looked in the art for specific dopamine agonists suitable for combination with anticholinergics, a[s] taught by Meissner, with the reasonable expectation of successfully preparing an effective combination therapy specific for a disorder".

Applicants respectfully traversed that rejection.

Applicants' invention relates to novel pharmaceutical compositions based on anticholinergics and dopamine agonists in the treatment of respiratory diseases. In particular, the claimed invention recites a pharmaceutical composition comprising one or more anticholinergics selected from tiotropium and oxitropium (optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of racemates thereof, and each optionally in the form of solvates or hydrates thereof) with one or more dopamine agonists. Applicants discovered, unexpectedly, that such

compositions exert a synergistic effect when administered to treat inflammatory or obstructive diseases of the respiratory tract.

Reiss et al. refers to a method for treating COPD with a composition comprising muscarinic M3 receptor agonists agents such as the quarternary ammonium compounds ipratropium bromide, oxitropium bromide and tiotropium bromide and at least one therapeutic agent selected from $\beta 2$ agonists, antitussive, corticosteroid, decongestant, histamine H1 antagonist, dopamine **antagonist**, leukotriene antagonist, 5-lipooxygenese inhibitor, phosphodiesterase IV inhibitor, VLA-4 antagonist, and theophylline. Although Reiss et al. refers to the desirability of combining a muscarinic M3 receptor antagonist with another active agent, in whatever of the many combinations available according to Reiss et al., none of the combinations are directed at the use of a dopamine **agonist**, such as pramipexole or talipexole, let alone the administration of such combinations by inhalation.

Meissner et al. refers generally to the use of new anticholinergic compounds of Formula 1 [0002] to treat COPD and asthma. Meissner et al. does not refer to or suggest the combination of salts of tiotropium or oxitropium with dopamine agonists or to the synergistic therapeutic effect produced by administration thereof. Furthermore, given the inherent variability of the activity of individual pharmaceutical chemicals when placed in a biological environment, it is impossible to predict the effect of the claimed combination (e. g., whether mutually inhibitory or not) from Meissner, et al.

Thus, there is no dopamine agonist nexus to suggest combining the muscarinic M3 receptor of Reiss et al. with the anticholinergics of Meissner et al. Accordingly, the rejection of claims 1, 5-9, 12-18, 21-22, 45 and 48-50 as obvious over the combined teachings of Reiss et al. in view of Meissner et al. should be reconsidered.

Claims 19-20 were "rejected under 35 U.S.C.§103(a) as being unpatentable over the combined references [as applied above], and further in view of Schmelzer et al (2002/0193392 A1)". Though conceding the absence of any disclosure in Reiss et

al. or Meissner et al. regarding preferred particle size, with the addition of Schmelzer et al., it was alleged to

> "have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the teachings of the combined references on compositions and method of treating respiratory disorders by administering a combined active agent formulation via inhalation by implementing the preferred particle size as taught by Schmelzer because of successfully preparing a formulation that would reach the desired site".

Applicants respectfully traversed that rejection.

Schmelzer et al. refers to a pharmaceutical composition comprising tiotropium salt and a salmeterol salt in which "the adjuvants have a maximum mean particle size of up to 250μm..." [0028]. Neither Schmelzer nor Reiss et al. mention anything about pharmaceutical combinations with dopamine agonists. Furthermore, all of the arguments (supra) made for the primary references can be applied against and overcome this rejection where there is no disclosure or suggestion of the claimed combination.

Accordingly, the rejection of claims 19-20 as obvious over Reiss et al., Meissner et al., in further view of Schmelzer et al. should be reconsidered.

In light of the foregoing remarks and amendments, early and favorable treatment on the merits is earnestly solicited.

Respectfully submitted,

Michael P. Morris

Michael P. Morris
Reg. No. 34,513

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
Ridgefield, CT 06877
Tel: 203-798-5285